Turk J Gastroenterol *2016; 27: 205-6*

Sofosbuvir and Velpatasvir: A complete pan-genotypic treatment for HCV patients

Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med 2015; 373(27): 2599-607.

Hepatitis C, a blood-borne virus responsible for inflammation of the liver, is characterized by six major genotypes, 1-6. Generally, Hepatitis C Virus (HCV) infected patients, of which there are close to 200 million worldwide, have been diagnosed with one primary genotype, rather than a combination of genotypes. While genotypes 1-3 are spread worldwide, with Genotype 1 accounting for over 60% of global HCV infections, genotypes 4-6 have maintained a geographic isolation in North Africa, South Africa, and South-East Asia, respectively.

As it stands, patients pursue treatments in hopes of killing HCV and stymieing liver damage. Unfortunately, medication profiles have been complicated by the HCV genotype and subtype, prior treatment regimens, and the presence of cirrhosis. While prior therapies focused on combinations of protease inhibitors, pegylated interferons and ribavirin, current therapy regimens have placed an emphasis on direct-acting oral antivirals.

Remarkably, researchers have identified a pan-genotypic treatment regimen producing significantly higher sustained virologic response (SVR) rates among patients classified by HCV genotypes 1-6 via a single tablet containing velpatasvir, an NS5A inhibitor, and sofosbuvir, an NS5B polymerase inhibitor. Feld et al. (1) carried out a double-blind, placebo-controlled study of 624 patients with chronic HCV spanning genotypes 1,2,4,5 and 6 (1). Conducted over a 12-week period, patients were randomly assigned to receive once-daily a tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir (n=624) or a placebo (n=116). Of these patients, 19% were noted to have compensated cirrhosis and 32% had had no SVR in prior HCV treatments containing interferons. Furthermore, 51% of those reporting prior failed HCV treatment had sustained a virologic relapse.

Following the 12-week study period, Feld et al. observed substantially higher SVR rates than expected across the board. Having set an overall baseline goal of 85% SVR (less than 15 IU of HCV RNA levels/mL at 12 weeks following treatment), they reported a 99% SVR (95% CI, 98 to >99) for the patients assigned to the sofosbuvir-velpatasvir tablet. Broken down by HCV genotype and subtype, the rates were still marvelously high: 98% (95% CI, 95 to >99) in patients with genotype 1a infection, 99% (95% CI, 95 to 100) with genotype 1b, 100% (95% CI, 97 to 100) with genotype 2, 100% (95% CI, 97 to 100) with genotype 4, 97% (95% CI, 85 to >99) with genotype 5, and 100% (95% CI, 91 to 100) with genotype 6 (1).

The SVR rate also remained relatively high regardless of whether patients suffered from cirrhosis or had received prior HCV treatments. Of those suffering from cirrhosis, 120 out of the 121 (99% [95% CI, 95 to >99]) had a SVR while of the 501 patients free of cirrhosis, 496 (99%, [95% CI, 98 to >99]) were noted to have a SVR. Likewise, of the 201 patients with prior HCV treatment experience, 200 (>99% [95% CI, 97 to 100] had a SVR while of the 423 treatment-naive patients, 418 (99% [95% CI, 97 to >99]) had a SVR. Amazingly, only two patients, both of whom were infected with genotype 1, receiving a sofosbuvir-velpatasvir tablet (n=624) had a virologic failure while only 15 patients (2%) had serious adverse health effects (1). Such data speaks volumes, underlining the superior ability of a joint sofosbuvir-velpatasvir prescription to sustain effective, long-term HCV treatment across five of the six major genotypes.

Though genotype 3 was not explicitly considered within this study, a supplementary study comparing genotype 2 and 3 patients obtained similarly high results of SVR rates regardless of the presence of compensated cirrhosis or prior failed HCV treatment (2). Patients were randomly assigned to receive either of two treatments: a once-daily, single tablet of sofosbuvir (400 mg) and velpatasvir (100 mg) or 400 mg of sofosbuvir and a body-weight dependent amount

of ribavirin. Following a period of 12 weeks (24 weeks for genotype 3 patients on sofosbuvir-ribavirin), Foster et al. (2) reported a SVR rate of 99% (95% CI, 96 to 100) among genotype 2 patients (n=134) receiving sofosbuvir–velpatasvir, as compared with 94% (95% CI, 88 to 97) receiving sofosbuvir–ribavirin (n=132). A substantially steeper SVR rate difference was noted between genotype 3 patients receiving sofosbuvir–velpatasvir (n=277, 95% [95% CI, 92 to 98]) and sofosbuvir–ribavirin (n=275, 80% [95% CI, 75 to 85]). Furthermore, SVR rates of cirrhosis patients were substantially higher in the sofosbuvir-velpatasvir group, 91%, as compared to the sofosbuvir-ribavirin group, 66%. Moreover, genotype 3 patients having both cirrhosis and prior failed HCV treatments were found to have an 89% SVR rate upon completion of their sofosbuvir-velpatasvir regimen as compared to 58% in the sofosbuvir-ribavirin group (2).

It was noted by Foster et al. (2), that only six genotype 3 patients (2%) suffered serious adverse health effects following treatment with sofosbuvir-velpatasvir while many more were affected in the sofosbuvir-ribavirin group (15 patients, 5%). Further, ribavirin-specific side effects such as insomnia, irritability and cough were more frequent in genotype 3 patients receiving sofosbuvir-ribavirin over sofosbuvir-velpatasvir.

All in all, among both studies, a treatment regimen focused on a single tablet administered once-daily of sofosbuvir-velpatasvir seemed to provide significantly increased, and rather similar, SVR rates among all six genotypes when compared to present, genotype-specific medications. While the teratogenic, hematologic and toxic side-effects of ribavirin have been well documented, the sofosbuvir-velpatasvir regimen had only a few casualties among all genotypic patients with more common adverse effects including headaches, fatigues or nausea.

Ultimately, the lack of an equally effective pan-genotypic HCV medication has spurred research on towards new heights with the promising results of sofosbuvir-velpatasvir providing a glimmer of hope in doing away with pretreatment genotype testing while potentially expanding the reach of treatments to low-and-middle income areas of the world tormented by the absence of an HCV vaccine.

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Received: January 28, 2016 Accepted: February 2, 2016

DOI: 10.5152/tjg.2016.160000

REFERENCES

1. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med 2015; 373: 2599-607. **[CrossRef]**
2. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med 2015; 373: 2608-17. **[CrossRef]**